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α-SUBSTITUTED SULFONAMIDES AND SULFONIC ACIDS. I. α-NITRO DERIVATIVES.

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During the past several years, there has been considerable interest in the synthesis of α-amino-, α-oximino-, α-hydroxylamino-, and other α-substituted acids as potential antitumor and antihypertensive agents.

In contrast to the extensive knowledge of α-carboxylic acids, little is known about α-functionally substituted sulfonic acids and sulfonamides.

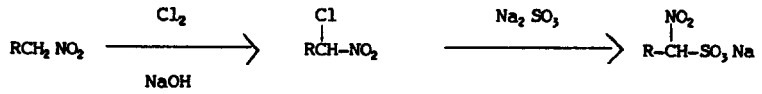
We wish to report the synthesis of α-nitrosulfonamides and sulfonic acids.

Prior to this work, no α-nitrosulfonamide was known, and only one α-nitrosulfonic acid of proven structure had been reported (nitromethanedisulfonic acid, $NO_2CH(SO_3H)_2$, prepared by Rathke in 1872 (1)).

Terent'ev and co-workers (2), in 1953, reported the sulfonation of nitromethane and nitrocyclohexane in 6 and 16% yields, respectively. No evidence was presented other than a barium analysis on the salt. Our repeated attempts to duplicate these experiments failed.

The reaction of nitroalkanes with sulfur dioxide and chlorine, in the presence of ultra-violet light, to give α-nitroalkanesulfonyl chlorides is claimed in a patent in 1955 (3). No physical constants for the claimed products are given, and the yields reported are inconsistent with the quantities of reactants employed. In our attempts to duplicate this reaction using nitroethane, the nitroethane was essentially quantitatively recovered.

It has now been found that α-halonitro compounds (readily prepared by halogenation of nitro compounds in alkaline solution (4)) react smoothly with sodium sulfite to give α-nitrosulfonates:



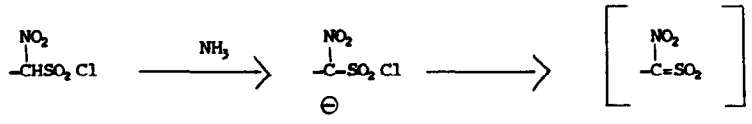
In a typical preparation, equimolar amounts of α-chloronitroethane (5) and sodium sulfite in 50% aqueous methanol were heated for 3 hours. The solution was concentrated to dryness and the salt recrystallized from ethanol, m.p. 118-20°. The compound deflagrates on a hot plate. The salt is very soluble in methanol and water.

The n.m.r. in D_2O confirms the structure: δ 1.85 (3H doublet), δ 5.78 (1 quartet); when treated with NaOD, the α-hydrogen is lost and the n.m.r. of the resulting aci form shows only a 3H singlet at δ 2.17 (6). The salt of the aci form was prepared by adding one equivalent of sodium methoxide to a solution of the mono sodium salt in methanol (6).

The free acid can be obtained either by passing hydrogen chloride into a methanolic solution of the sodium salt, or by passing an alcoholic solution of the salt over a strong acid ion-exchange resin. The acid has thus far only been isolated as an oil which decomposes on standing. It can be reconverted to the original salt on treatment with dilute sodium hydroxide.

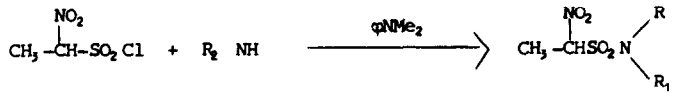
Conversion to the sulfonyl chloride proved very difficult. Most of the usual methods (thionyl chloride, oxalyl chloride, or phosphorus oxychloride in the presence or absence of amines or DMF) gave extremely poor yields. The sulfonyl chloride, b.p. 81-83° (2 mm), was ultimately obtained in 35% yield by heating the salt with phosphorus pentachloride in phosphorus oxychloride (6).

Conversion of the sulfonyl chloride to a sulfonamide also proved to be surprisingly difficult. No product could be isolated from reaction with excess ammonia, dimethylamine or piperidine under various conditions. This may be due to ready formation of a sulfene because of the strong electronegative alpha substituent:



This highly reactive sulfene then may have undergone secondary reactions.

When the α-nitrosulfonyl chloride was reacted with amines under very mildly basic conditions, a sulfonamide could be isolated:



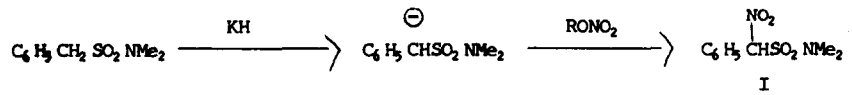
R=H, R_1 = $C_6H_5CH_2CH_2$-, m.p. 110-11°

R=CH_3, R_1 = C_6H_5, b.p. 121° (0.1 mm.)

Attempts are being made to trap the proposed nitro-sulfene intermediates.

Another route to α-nitrosulfonamides has also been developed.

The α-hydrogen of a sulfonamide can be removed by treatment with potassium hydride (with more difficulty by sodium hydride or sodamide); the resulting carbanion reacts smoothly with nitrate esters to give an α-nitrosulfonamide. In this way, N,N-dimethylbenzylsulfonamide was



nitrated in 75% yield using ethyl nitrate, and in 25% yield using acetone cyanohydrin nitrate (7) to give I, m.p. 59-60° (6). In $CDCl_3$, the α-hydrogen appears as a singlet at δ 6.50 p.p.m. Attempts to prepare α-nitrosulfonamide by direct nitration of alkylsulfonamides using fuming nitric acid, or vinylsulfonamides using dinitrogen trioxide, failed.

The α-nitrosulfonamides are fairly strong acids (pKa 5.33) soluble in aqueous bicarbonate.

References

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5. We are indebted to Mr. S. A. Walker of Aerojet-General Corp. for supplying us with samples of α-chloronitroethane.
6. Gave satisfactory elemental analyses.
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